UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,340	09/28/2005	Tadashi Yamazaki	081356-0249	4619

22428 7590 10/05/2009

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
10/05/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,340	YAMAZAKI ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2009 and 26 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-31* is/are rejected.

7)☒ Claim(s) *24-28 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

9DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/29/2009 has been entered.

2. In the submission of 7/29/2009, claims 11-15 were canceled and new claims 16-23 were added. In a supplemental response filed 8/26/2009, claims 16-23 were canceled and new claims 24-31 were added. Accordingly, claims 24-31 are currently pending and subject to examination below.

Priority

3. The present application was filed on 9/28/05 as a National Stage (371) application of PCT/JP04/04606, filed 3/31/04. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Japanese Application No. 2003-094059, filed on 3/31/03.

Objections/ Rejections Withdrawn

4. The objection to the specification has been withdrawn in response to Applicant's amendments thereto.

5. The objection to claim 11 and the rejections of claims 11-15 have been withdrawn in view of Applicant's cancellation of these claims.

Claim Objections

6. Claims 24-28 and 31 are objected to because of the following informalities:

7. Claim 24 recites an immunoassay method for measuring lipoprotein(a). The body of the claim sets forth a step (b) in which absorbance or light-scattering variation is observed. Based on the specification, it is clear that this detection of absorbance or light-scattering is being used to indicate the presence of lipoprotein(a). However, this is not clearly explained in the claim, which does not make explicit how observation of absorbance or light scattering relates to measurement of lipoprotein(a). It is suggest that the claim recite either an active method step in which lipoprotein(a) is measured or alternatively, a correlation step that describes how the results of the immunoassay method relate back to lipoprotein(a) measurement.

8. In claim 24, line 5, "an amount" should apparently read "amounts of" since two specified amounts follow.

9. Claims 25-26 and 31 refer to "the antibody" in the singular, while independent claim 24 invokes "anti-lipoprotein(a) antibodies" in the plural. Applicant is requested to amend the claims for proper subject-verb agreement.

10. Claims 25-28 recite "the antigen-antibody reaction". It is presumed based on the specification that Applicant refers to the reaction between lipoprotein(a) in the biological sample and the anti-lipoprotein(a) antibodies on the latex particles. However, this is not made clear because claim 24 does not explicitly state that such a reaction takes place or refer to lipoprotein(a) as an "antigen". Similarly, these dependent claims also refer to "a reaction solution" or to "the reaction solution". Applicant presumably intends to refer back to the

"mixture" of claim 24. Applicant is requested to employ consistent terminology throughout the claims in order to avoid confusion.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 26 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claim 26 recites a method according to claim 25, wherein the amount of the antibody added is "from 0.16 mg/mL inclusive" in the reaction solution at the time of the antigen-antibody binding. It is not clear what amount(s) are intended. In reciting "from 0.16 mg/mL" the claim appears to invoke a range, but no other limit is specified to define the boundaries of the range. It is therefore not clear how claim 26 differs from and further limits claim 25. Further, it is unclear what is meant by the term "inclusive" in the context of claim 26. In claim 28 the term "inclusive" is taken to mean that the end points of the range are included, but here there is only one end point specified. For the purposes of examination, claim 26 was interpreted in the same manner as claim 25, i.e. to refer to a range greater than or equal to 0.16 mg/mL.

15. Claim 29 recites a method "according to anyone of claim 16". The claim is indefinite because it refers to a canceled claim. For the purposes of examination, the claim was assumed to recite a method according to claim 24.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 24-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borque et al. ("Automated turbidimetry of serum lipoprotein(a)" Eur J Clin Chem Clin Biochem. 1993 Dec;31(12):869-74) in view of de Steenwinkel et al. (US 4,362,531), Metzner et al. (US 6,447,774), and Schmitdberger et al. (US 5,180,679).

Borque et al. teaches a turbidimetric immunoassay for quantifying lipoprotein(a) using latex particle agglutination (abstract and especially at page 869, "Summary"). The immunoassay

involves contacting the sample with rabbit polyclonal IgG antiserum against human lipoprotein(a) coated onto latex particles (see pages 869-870, "Antibody", "Latex reagent", and "Assay Procedure"). The amount of lipoprotein(a) is then determined by observing the mixture for turbidity due to latex particle agglutination using an automatic analyzer, which measures absorbance at 700 nm (see page 870, "Assay procedure"; page 871, "Correlation"; Figure 1; and page 872, right column).

With respect to the recitation that "whereby said variation is a function independent of lipoprotein(a) phenotype", claim interpretation is as follows. In describing the claimed invention, Applicants discuss how a measurement value obtained "independently of the phenotype of a molecule used as a reference material" means that a nearly identical measurement value is obtained even if the phenotype of a molecule used as the reference material has changed (specification, paragraph bridging pages 11-12). Further, it is discussed how the resulting measurement would "have a high correlation" with measurements obtained by ELISA (ibid and paragraph bridging pages 10-11). Consequently, the indicated "whereby" clause is not taken to mean that measurement would be totally insensitive to lipoprotein(a) phenotype, but rather that nearly identical measurement values would be obtained even if different phenotypes of lipoprotein(a) were used; and that such values would have a high correlation with measurements made by ELISA.

In this regard, Borque et al. discuss how the heterogeneity caused by genetic isoforms of apolipolipoprotein(a) (i.e., lipoprotein(a) phenotype) contributes only slightly to the overall size heterogeneity since the assay uses large latex particles (see page 872, right column). Furthermore, Borque et al. compared results obtained using their latex turbidimetric method with

results obtained by ELISA. As depicted in Figure 3, the former had a high correlation with the latter (see panels (c) and (d), in which measurements obtained by the two methods correlated with two different ELISA methods with an r value of 0.978).

Because Borque et al. indicate that lipoprotein(a) phenotype contributes only slightly to the overall size heterogeneity, and further teach that their measurements correlated highly with those obtained by ELISA, there is a strong scientific basis to believe that the resulting measurement values obtained when using different lipoprotein(a) phenotypes as reference material would be nearly identical and thus "independent of lipoprotein(a) phenotype". See MPEP 2112.

Applicant is also reminded that claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. See MPEP 2111.04. In the instant case, the conclusory statement "whereby said variation is a function independent of lipoprotein(a) phenotype" does not clearly invoke any additional method steps or elements, but simply appears to state a characterization or conclusion of the results of those steps earlier recited, i.e. a necessary effect of the preceding method steps. Notwithstanding the above, therefore, the "whereby" statement is not considered to clearly further limit the method defined by the claim. See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited."). In other words, it is also presumed that an assay method performed using the indicated reagents of step (a) in their recited amounts

would necessarily exhibit absorbance light-scattering variation that is independent of lipoprotein(a) phenotype.

The teachings of Borque et al. differ from the claimed invention in that (1) the reference fails to specifically teach adding a basic amino acid to the assay system and (2) the reference is silent as to the particular concentrations of the antibodies used in the assay.

With respect to (1), de Steenwinkel et al. also relates to particle agglutination immunoassays and teaches that undesired interference effects in such assays due to non-specific protein-protein interactions can be reduced or overcome by including in the assay mixture a chaotropic or chaotropic-like agent (the abstract; column 1, lines 18-41; column 2, line 42 to column 4, line 50).

However, de Steenwinkel et al. do not specifically exemplify chaotropic agents that are basic amino acids.

Metzner et al. teaches that known chaotropic agents include arginine (column 1, lines 55-56; column 2, lines 12-13).

Therefore, it would have been obvious to one of ordinary skill in the art to add a chaotropic agent to the agglutination immunoassay of Borque et al. because de Steenwinkel et al. taught that such agents reduce or overcome interferences in particle agglutination immunoassays. It would have been further obvious to employ the basic amino acid arginine as the chaotropic agent in the method of Borque et al. and de Steenwinkel et al. because Metzner et al. taught that arginine is known to be a chaotropic agent. The selection of a known material for its known purpose would have been obvious.

Furthermore, de Steenwinkel et al. teach that the amount of chaotropic agent to be added to agglutination immunoassays should be checked for individual cases, since the optimum amount may vary (column 3, lines 29-38). Such teachings indicate that the amount of a chaotropic substance was recognized in the art to be a result-effective variable.

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05.

In addition, it is also noted that de Steenwinkel et al. provides guidance with regard to the selection of appropriate amounts of chaotropic agent to be used, teaching that in most cases, amounts of from about 0.5 up to about 2M are satisfactory (column 3, lines 34-36). It is asserted that the molecular weight of arginine was known in the art to be 174.2 g/mol. Since 1% of a solute is equal to 1 g per 100 ml, this would mean that in the case of arginine the range of 0.5-2M taught by de Steenwinkel et al. would correspond to 8.7%-34%[1], a range which overlaps that claimed instantly.

[1] (0.5 moles/L) x 174.2 g/mol = 87.1 g/L and (2 moles/L) x 174.2 g/mol = 348.4 g/L
1 g/ 100 mL = 1%
87.1 g/L = 8.71 g/ 100 mL = 8.7% and 348.4 g/L = 34.8 g/ 100 mL = 34%

Therefore, absent evidence of criticality for the currently claimed amounts it would have been obvious to one of ordinary skill in the art to arrive at the claimed amounts of arginine (i.e., about 12% by weight or greater) out of the course of routine optimization, and in particular by following the guidance of de Steenwinkel et al. regarding suggested amounts of chaotropic agent.

With respect to (2), Borque et al. do not explicitly state what the final concentration of the antibody in the assay mixture was, but do indicate that the amount of antibody added was adjusted by providing antibody in a protein/ latex ratio of 1/10; 30 ml of a 0.5% particle solution was then added to the assay (page 870, "Latex Reagent" and "Assay procedure").

Schmidtberger et al. also relates to particle agglutination immunoassays and teaches that different amounts of antibody can be bound to the particles in order to influence the time at which agglutination occurs (column 2, lines 13-62).

Therefore, given that the amount of antibody used in a particle agglutination immunoassay was recognized in the art to be a result-effective variable (as taught by both Borque et al. and Schmidtberger et al.), it would have been further obvious to one of ordinary skill in the art to employ polyclonal IgG antiserum against human lipoprotein(a) in amounts falling within the claimed ranges of 0.15 or 0.16 mg/ml or greater out of the course of routine optimization.

With respect to claim 30, as the methods of Borque et al. measured whole lipoprotein(a) molecules (page 872, right column), such measurements may be said to be "on a molecular basis" when this terminology is given its broadest reasonable interpretation.

With respect to claim 31, Borque et al. teaches a polyclonal antibody (see page 869, "Antibody").

Response to Arguments

19. In the Reply of 8/26/2009, Applicant presented new claims 24-31 and argued that the present application is in condition for allowance (Reply, page 4). Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

20. In the Reply of 7/27/2009, Applicant presented arguments with respect to the rejections of claims 11-15 under § 103 as being unpatentable over Borque et al. in view of de Steenwinkel et al., Metzner et al., and Schmitdberger et al. Applicant's arguments are technically moot as claims 11-15 have been canceled. However, certain of Applicant's arguments have been addressed below as they pertain to the rejections of claims 24-31 over these references as set forth above.

Applicant argues that the claimed assay measures a plurality of lipoprotein(a) phenotypes explicitly discounted by Borque et al., pointing to page 872, lines 15-17 pf the reference (Reply, page 5).

Initially, it is noted that the instant claims do not recite or clearly require measurement of a plurality of lipoprotein(a) phenotypes. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, Examiner disagrees with Applicant's analysis of Borque et al. The passage indicated by Applicant contrasts the large size of the latex particles being used for the assay with the comparatively small differences in size among different apolipoprotein(a) isoforms. In other words, the large particles dampen the smaller size differences among the phenotypes. There is nothing in Borque et al. to suggest that their method does not measure the plurality of isoforms, as argued by Applicant. Rather, this passage indicates to the contrary that the different apolipoprotein(a) isoforms would in fact all bind to the particles, and that as a result, their comparatively small differences in size become less significant because they are bound to much larger particles.

Applicant further argues that de Steenwinkel et al. teaches chaotropic agents for the purpose of reducing weak protein-protein interactions (i.e., to reduce non-specific binding), while the instant invention employs chaotropic agents in order to increase protein-protein interactions, thereby increasing the detectable interaction between the antibody and the various lipoprotein(a) phenotypes (Reply, page 5, last paragraph).

This is not found persuasive because de Steenwinkel et al. draw a clear distinction between *weak* protein-protein interactions and the desired antibody-antigen *immunospecific* reaction under study, providing guidance with regard to what concentrations of chaotropic agent to use (see especially columns 3-4). As such, the reference does not broadly teach using chaotropic agents to reduce any type of protein-protein interaction, but only those of a weak nature that interfere with the assay.

Furthermore, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when

the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Even if de Steenwinkel et al. do not explicitly teach using chaotropic agents to increase specific protein-protein interactions, this feature would necessarily follow since a chemical composition and its properties are inseparable.

Applicant also appears to argue for unexpected results, in that that increasing the content of chaotropic agent increases the detectable interaction between the antibody and the various lipoprotein(a) phenotypes (Reply, page 5, last paragraph).

Whether evidence shows unexpected results is a question of fact and the party asserting unexpected results has the burden of proving that the results are unexpected. In re Geisler, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362, 1364-5 (Fed. Cir. 1997). The evidence must be (1) commensurate in scope with the claimed subject matter, In re Clemens, 622 F.2d 1019, 1035, 206 USPQ 289, 296 (CCPA 1980), (2) show what was expected, to "properly evaluate whether a … property was unexpected", and (3) compare to the closest prior art. Pfizer v. Apotex, 480 F.3d 1348, 1370-71, 82 USPQ2d 1321, 1338 (Fed. Cir. 2007). Consequently, the burden of demonstrating unexpected results rests on the party asserting them, and "it is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an unexpected difference." In re Klosak, 455 F.2d 1077, 1080 (CCPA 1972).

In the instant case, de Steenwinkel et al. teach that interference (due to non-specific binding of non-analyte components) reduces the sensitivity of the assay (see column 1, lines 57-60). As such, no evidence of unexpected results is apparent because the reduction of such background interference in an assay (which is the purpose for which chaotropic agents are taught by de Steenwinkel et al.) would be *expected* by those of ordinary skill in the art to increase the

sensitivity of the assay (i.e., to increase the detectable interaction between the antibody and the analyte).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641